Pathophysiology and Therapeutic Targets for Ischemic Stroke

STEVEN R. LEVINE, M.D.

Cerebrovascular Education Stroke Program, Mount Sinai School of Medicine, Department of Neurology, New York, New York, USA

Summary: The increased risk for stroke among those who have had a previous stroke or transient ischemic attack (TIA) and the tremendous burden of disability among stroke sufferers make both primary and secondary preventative strategies imperative. An understanding of the pathophysiology of stroke and TIA can help identify appropriate therapeutic targets.

Stroke and Heart Disease

Shared Pathology and Risk Factors

Underlying atherosclerosis, which plays a significant role in both ischemic stroke and myocardial infarction (MI), is similar in both conditions. Despite this similarity, however, these two disease states are characterized by distinct differences in pathophysiology that go beyond the mere location of the thrombus. Coronary artery lesions tend to be more fibrotic than those found in the cerebral vasculature.^{1,2} Stroke patients are an extremely heterogeneous group compared with those who have had an MI. There is a variety of sources for the thrombus as well as numerous areas in which ischemic occlusion can occur. The evolution of the consequences of the ischemic event also differs in stroke and MI. Stroke pathology pursues a much longer course than MI, with secondary damage and metabolic sequelae occurring at times up to a month after the initial event.³ The neurological complications and clinical manifestations following a stroke vary considerably as

well, depending upon which areas of the brain were affected and to what degree. Patients may suffer from any combination of cognitive, motor, visual, sensory, language, speech, or mood deficits. Deficits can be discrete or global. Finally, despite the pervasive notion that stroke patients are at increased risk for acute MI, in up to 75% of stroke survivors a subsequent cardiovascular event could be another stroke.⁴

However, both stroke and MI share many risk factors. Hypertension and diabetes mellitus are important modifiable risk factors for both stroke and heart failure.⁵ In fact, cardiovascular disease, including stroke and heart disease, is the primary cause of death in persons with diabetes.⁶ Hyperlipidemia is an accepted risk factor for coronary artery disease, and its contribution to ischemic stroke is also important.^{7–10} Data from studies indicate that use of the beta-hydroxy-beta-methylglutaryl-CoA reductase inhibitors or statins (cholesterol-lowering drugs) offers stroke protection and reduces the amount of carotid atheroma, although the mechanisms involved are unclear.^{7–10}

Lifestyle factors, such as obesity and smoking, and use of a number of chemical substances, including alcohol and both legal and illegal drugs, have been associated with cardiovascular disease in general and stroke in particular.^{7, 11, 12} Some prescription medications have been associated with an increased incidence of stroke. In the past, early-generation oral contraceptives were found to increase stroke risk,¹³ and controversy has surrounded hormone replacement therapy (HRT), with recent findings from the Hormone and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) indicating an increased stroke and heart attack rate among women using HRT.^{14–16} Adding to the mounting evidence, the Women's Estrogen Stroke Trial (WEST) failed to show that HRT provided protection from recurrent stroke. Recurrent stroke was in fact more severe in the HRT group than in those taking placebo.¹⁷

Illicit drugs such as cocaine and amphetamines have been implicated in both stroke and heart disease.^{12, 18} Elevated levels of homocysteine may be a factor in both disorders as well.^{7, 11} As is true of many chronic illnesses, genetics play a substantial role in both stroke and heart disease. The underlying mechanisms of atherosclerosis and hypertension are determined in part by genetics. Evidence indicates that both eating patterns and heredity affect blood cholesterol levels, and atherosclerosis or its precursors have been found in young persons.¹¹

Address for reprints:

Steven R. Levine, M.D.
Professor of Neurology
Mount Sinai School of Medicine
Department of Neurology
1 Gustave L. Levy Place
Box 1137
New York, NY 10029, USA
e-mail: steven.levine@mssm.edu

The Interrelationship between Heart Disease and Stroke

A number of heart conditions play a role in stroke. Strokes that follow acute MI are most often embolic, usually originating from the left ventricular mural thrombi, although atherothrombotic strokes secondary to hemodynamic compromise occur as well.¹⁹ The presence of atrial fibrillation (AF) places a patient at increased risk for stroke. Cardioembolic strokes constitute 20% of ischemic strokes,²⁰ and nearly half of these occur in patients with AF.²¹ Furthermore, more than two-thirds of strokes in patients with AF are cardioembolic.⁷ In patients with nonvalvular AF, the annual risk of stroke is 3 to 5%.^{7, 22} Ischemic stroke also is a well-established complication of valvular disease, involving either native or prosthetic valves.^{7, 19} Other cardiac conditions associated with stroke include patent foramen ovale, atrial septal defect, and atrial septal aneurysm.^{7, 23}

Stroke Subtypes

About 80 to 85% of strokes of known etiology are ischemic, with the remaining 15 to 20% being hemorrhagic.²⁴ Hemorrhagic strokes are either subarachnoid or intracerebral and originate with the rupture of a cerebral blood vessel or an aneurysm within the blood vessel, resulting in an accumulation of blood and compression of brain tissue.^{21, 25, 26} Intracerebral hemorrhages are more common than subarachnoid hemorrhages, with 37,000 cases occurring each year in the United States, compared with 25,000 cases of subarachnoid hemorrhage (Fig. 1).²⁷⁻³¹

Most ischemic strokes are embolic in nature, with an embolus or blood clot (or even atheroma) forming either within the cerebral arteries themselves or elsewhere in the body and migrating to the brain. Onset is usually rapid.²⁵ Ischemic strokes also can be caused by perfusion failure, which arises as the result of plaque buildup within the cerebral vessels, typically within the carotid arteries or the basilar artery.^{19, 25} The onset of symptoms may range from minutes to days.

FIG. 1 Frequency of first choice diagnosis. ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage. Reprinted from Ref. No. 31 with permission.

Aortic arch atherosclerosis has been implicated in brain infarction, particularly in stroke of unknown origin or cryptogenic stroke, which constitutes up to 30% of all stroke.^{26, 32} This condition is common in persons older than 60 years. Mural thrombi can develop and break away to travel to the brain or other organs; unstable ulcerated plaques may release atheromatous material that forms emboli as well.³³ Aortic arch plaques may also play a role in strokes that occur during coronary artery bypass graft surgery. Use of ultrasound monitoring techniques during cardiac surgery has detected emboli within the aorta and the middle cerebral arteries in the majority of patients.³⁴ The diameter of emboli visualized within the aorta is >0.2 mm. Emboli >1 mm in diameter could occlude a major cerebral artery and cause a noticeable infarct, while those <0.5 mm in diameter might cause microinfarcts in the terminal cortical arterioles.³⁴

Atherosclerotic lesions or plaques are not evenly distributed throughout the cerebral vasculature, but tend to develop in certain areas. Stenosis within the internal carotid arteries (ICA) appears most often at the common carotid artery bifurcation and the siphon, while in the middle cerebral artery (MCA) it tends to occur at the M1 segment. The vertebrobasilar circulation is most likely to be affected in the first and fourth segments of the vertebral artery and the first segment of the basilar artery.¹⁹

Infarctions in the anterior cerebral artery (ACA) territory often involve MCA territory infarction as well.³⁵ In the United States, ACA infarcts are most often cardioembolic or the result of ICA stenosis,³⁵ and in situ thrombosis of the ACA is rare in Western countries. However, this trend does not hold among Asian populations, in whom ACA as the result of local thrombosis is more common.³⁵ The MCA is the most commonly affected cerebral blood vessel in infarctions resulting from embolism or thrombosis, and strokes in this region may be superficial, deep, or both.³⁶ The posterior cerebral arteries (PCAs) supply parts of the thalamus and the cortical structures essential for vision, memory, and somatoesthetic perception. Because the PCAs are located at the terminal end of the vertebrobasilar artery system, they are often the target for thromboemboli from the heart, the aorta, and both extra- and intracranial vertebral arteries.³⁷ Imaging studies have shown that the most common cause of PCA infarcts is an intra-arterial embolism originating from atherosclerotic lesions of the vertebral and basilar arteries.³⁷ Although the neurological signs and symptoms associated with each of these types of infarct are diverse and of great interest, their description is beyond the scope of this article.

Lacunar strokes are associated with small penetrating vessel disease and are considered to have a higher prevalence of hypertension than other forms of ischemic stroke, although there is considerable controversy regarding this.^{23, 38, 39} It is rare for an embolism from the large arteries or the heart to be implicated in lacunar stroke.³⁸ The predominant mechanism appears to be in situ small-vessel disease (microstenosis), resulting in perfusion failure or microatherothrombosis. Hemodynamic factors as the consequence of large-vessel disease, such as carotid stenosis, occasionally are responsible.^{25, 38}

As with most lacunar strokes, border zone infarcts are the result of perfusion failure. Border zones are at higher risk for perfusion failure because they are located in the junctions between the territories supplied by the major cerebral arteries and thus receive the most marginal blood flow.⁴⁰ These infarcts account for about 10% of ischemic strokes. Studies have suggested that the combination of hypotension due to cardiac disease or other causes and severe extracranial carotid arterial stenosis is the primary risk factor for border zone infarcts.⁴⁰⁻⁴²

Transient Ischemic Attacks

Transient ischemic attack is defined as a brief period of focal loss of brain function attributable to ischemia and lasting < 24 h. A recent panel of experts called for a revised definition that requests a normal clinical neurological examination and brain imaging relevant to the symptoms.⁴³ *Amaurosis fugax*, or monocular blindness, is included under this rubric as well.^{44,45} The TIA shares the same risk factors and is caused by the same mechanisms that operate in ischemic stroke, with age being the most important risk factor for both.^{44,46} The incidence rate of TIA is about 40% that of stroke.⁴⁶

Most TIAs resolve within 30 to 60 min and *Amaurosis fugax* usually does so within 5 to 10 min. Despite the definition by duration, TIA represents one end of a spectrum that continues on into minor ischemic stroke. It poses a substantial risk for subsequent ischemic stroke, with the greatest risk occurring in the period immediately following the TIA.⁴⁷ Carotid artery disease accounts for nearly 80% of attacks.⁴⁶ Data from ultrasound studies have shown a correlation between greater plaque thickness and longitudinal plaque motion and increased likelihood of TIA, whereas stroke showed a stronger correlation with occlusion of the carotid artery and wider lesions.⁴⁸

The Role of Atherosclerosis

Atherosclerosis is estimated to lie at the root of 70% of all strokes⁴⁹ and is now believed to be a disease of chronic inflammation.⁷ Atheromatous plaques tend to develop at points of high shear stress and vessel bifurcations,^{1,50} and the vessels most likely to be affected in association with ischemic stroke are the extracranial internal carotid and vertebral arteries.⁷ Lesions may start as the result of endothelial surface injury. Cytokines, peroxides, and other substances excreted in response to injury may provoke endothelial cells to express P-selectin, intercellular adhesion molecule-1 (ICAM-1), and E-selectin, which in turn encourage leukocyte adhesion to the endothelial surface and subsequent migration into the intima, leading to fatty streak formation.^{1,7} As might be expected at the site of an injury, macrophages infiltrate fatty streaks and plaque and accumulate lipids, leading to the formation of foam cells.⁵¹ Thus, acute inflammatory responses may create a favorable environment for plaque generation and destabilization (Figs. 2 and 3).⁷

Although fatty streaks, the earliest form of atherosclerotic lesions, first appear in childhood, it is not until the third or fourth decade that fibrous or atheromatous plaques begin to appear.^{1,52} A fibrous cap, formed of proliferated smooth muscle cells and dense connective tissue, covers the lesion, which protrudes into the lumen of the vessel.¹ Beneath this cap lies a necrotic core of extracellular lipid (primarily cholesterol, cholesteryl esters), fibrin, cellular debris, foam cells, and plasma proteins.^{1,46} As plaques enlarge, thicken, and sometimes converge, they may cause stenosis and occlusion of the blood vessel.⁵¹ Plaques also may ulcerate, develop thrombosis or intraplaque hemorrhage, or calcify. Rupture can lead to the formation of an embolus.^{1,51} Involvement of the media may weaken the vessel wall and lead to formation of an aneurysm.⁵¹

FIG. 2 Atherosclerosis timeline. Reprinted from Ref. No. 52 with permission.

FIG. 3 A cell-based paradigm of arterial thrombosis. TF = tissue factor, TNF- α = tumor necrosis factor alpha, TAFI = thrombin activatable fibrinolysis inhibitor, PAI = plasminogen activator inhibitor. Reprinted from Ref. No. 53 with permission.

A complete understanding of the mechanisms involved in atherogenesis and in the destabilization of plaque will likely provide potential therapeutic targets. Although the factors that predispose a particular plaque to ulceration or rupture are not yet known, both plaque structure and composition as well as hemodynamics are likely involved.⁵¹ At this time it appears that rupture takes place at the junction of the fibrous cap and the normal surrounding intima.¹ Once the necrotic core is exposed to the bloodstream, its expression of tissue factor makes it highly thrombogenic.¹ A coagulation cascade may thus be initiated, leading to arterial occlusion.^{51,53}

Risk Factors and Possible Pathogenic Mechanisms

Endothelial injury can occur through a number of mechanisms. Many of the risk factors traditionally associated with stroke, such as hypertension, smoking, chronic diabetic hyperglycemia, and dyslipidemia, have been proposed as possible sources of endothelial injury. Over time, potassium channels, which appear to influence relaxation of the cerebral vessels, may be altered by chronic disease states such as hypertension, diabetes mellitus, and atherosclerosis.⁵⁴ Although the cerebral vasculature has a degree of adaptive capability, over time hypertension and associated shear forces may predispose blood vessels to injury through increased stress on the endothelium.⁵⁵ Animal models suggest that, in addition, hypertension may decrease plasma levels of thrombomodulin and induce a hypercoagulable state.⁵⁶

The macro- and microvascular complications associated with chronic diabetic hyperglycemia are evident from clinical studies, but the mechanisms involved are not well understood. However, recent evidence suggests that a hyperglycemic environment may damage vascular endothelial cells by increasing reactive oxygen species (ROS) production, which in turn can stimulate aldose reductase, protein kinase C, and diacylglycerol.⁵⁷ Elevations in plasma glucose levels also are associated with ICAM-1 level increases that decline in response to insulin treatment.^{58,59}

Hypercholesterolemia produces lesions with a higher lipid content.^{51,60} Induction of monocyte chemotactic protein (MCP-1) by oxidized low-density lipoprotein (LDL) cholesterol may assist monocyte diapedesis through the endothelium and into the intima.^{1,61} Oxidized LDL also contributes to the accretion of lipids within maturing foam cells.^{51,62,63} In addition, oxidized LDL is cytotoxic to endothelial cells and, because it inhibits the release of endothelial-derived relaxing factor, can alter the vasomotor properties of the arteries.^{51,64}

The role of alcohol in promoting stroke is controversial. Some studies have suggested a protective effect for moderate consumption, which may increase high-density lipoprotein (HDL) cholesterol and endogenous tissue plasminogen activator (t-PA).⁶⁵⁻⁶⁷ On the other hand, heavy alcohol consumption appears to increase hypertension and induce hypercoagulable states, cardiac arrhythmias, and reductions in cerebral blood flow (CBF).⁶⁷

The mechanisms by which smoking increases stroke risk are diverse as well. Smoking may increase coagulability, blood viscosity, and fibrinogen levels, enhance platelet aggregation, and elevate blood pressure.^{66,68} There is evidence as well that heavy smoking may create more fibrotic lesions.^{51,60}

More novel stroke risk factors include infection, homocysteine, C-reactive protein (CRP), and coagulation and platelet factors. A number of infectious agents have been proposed as possible causes of endothelial injury and initiators of a proinflammatory state, including cytomegalovirus (CMV), *Helicobacter pylori*, and *Chlamydia pneumoniae*. These are believed to induce chronic inflammation in the endothelium through the production of cytokines and free radicals and the stimulation of vascular smooth muscle cell, monocyte, and T-lymphocyte proliferation.⁶⁹ Epidemiologic links have also been suggested for periodontal disease, although the many organisms that colonize the oral cavity and the confounding factors of diet, smoking, and genetics make determining the relationship difficult.^{58,69} Although *C. pneumoniae* is the most promising candidate, the evidence implicating all these pathogens is far from conclusive and additional investigation is called for.^{7,69}

Homocysteine is believed to impair endothelial function, oxidize LDL, increase monocyte adhesion to the vessel wall, activate coagulation factors, and impair platelet function.⁶⁹ Data from a recent animal study have demonstrated that experimentally induced hyperhomocysteinemia in rats causes endothelial cell apoptosis and may reduce capillary cell density.⁷⁰ Investigators also found structural damage to the aorta, kidney, and renal ureter, which suggests that homocysteine-associated endothelial/epithelial damage is possible in multiple organ systems.⁷⁰ C-reactive protein, on the other hand, is believed to be more of a marker than a cause of dysfunction.⁶⁹

Primary abnormalities of coagulation and platelet function are implicated in only a small percentage of strokes.^{71,72} Several prospective studies demonstrated an association between the presence of antiphospholipid antibodies (aPL) and ischemic stroke,^{73,74} but the pathogenic mechanisms are unclear at this time.^{7,72} Many medications, including beta-lactam antibiotics, penicillins, cephalosporins, antihistamines, and nonsteroidal anti-inflammatory drugs, can disrupt platelet function.⁷²

Pathophysiology of Acute Ischemic Stroke

Ischemia exists along a continuum, from CBF reductions of just < 50% of normal (borderline ischemia) to CBF 20% of normal (severe ischemia), which occurs when perfusion pressure falls to ≤ 30 mmHg.⁷⁵ At that point, bioenergetic failure is triggered, reductions in tissue concentrations of phosphocreatine and adenosine triphosphate (ATP) occur, and both adenosine diphosphate (ADP) and adenosine monophosphate (AMP) increase. This failure initiates a chain of events that seriously threatens the survival of neurons even when the ischemia persists for only 4 to 6 min.⁷⁵

Bioenergetic Failure

Although glucose is the sole energy source used by brain tissue under normal circumstances, glucose supply is not rate limiting and normal functioning can continue even if concentrations fall to half of normal.⁷⁵ On the contrary, high levels of plasma glucose in the immediate preischemic period can prove deleterious.⁷⁵ Although it would initially seem that oxygen supply is most crucial, a decrease in arterial hemoglobin concentration to 20% of normal does not have a significant effect on the cerebral energy state. In fact, cerebral ischemia (reduced blood flow) is far more damaging than simple hypoxia.⁷⁵

Indeed, CBF appears to be the critical determinant of bioenergetic failure, as a reduction in flow fails to remove potentially toxic waste products, such as nitric oxide (NO) and ROS, and provokes possibly destructive interactions between endothelial cells and blood-borne elements such as platelets and polymorphonuclear neutrophil (PMN) leukocytes.⁷⁵⁻⁷⁸ These leukocytes may impede microvascular perfusion by adhering to activated endothelial receptors and, in conjunction with thrombocytes, may trigger an inflammatory response that can

FIG. 4 Major pre- and postsynaptic ion channels. AMPA = amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid, FFA = free fatty acid, LPL = lipoprotein lipase, NMDA = *N*-methyl-D-aspartate, PAF = paroxysmal atrial fibrillation, XDH = xanthine dehydrogenase, XO = xanthine oxidase. Reprinted from Ref. No. 75 with permission.

adversely affect microvascular tone and blood brain barrier (BBB) function. Subsequent swelling of endothelial cells can further compromise capillary perfusion.^{75, 79, 80}

The bioenergetic state remains stable until a threshold is reached (≤ 30 mmHg), at which point a depolarization wave causes a massive flux of K⁺ and Ca²⁺, activating ATPases and consuming what energy stores are left.⁷⁵ Furthermore, acidosis and cellular influx of Ca²⁺ inhibit the electron transport in the mitochondria, thereby uncoupling oxidative phosphorylation from oxygen consumption.⁷⁵ Ion cycling may prevent restoration of the normal bioenergetic state, while cellular uptake of Ca²⁺, Na⁺, and Cl⁻ induces additional harmful cascades (see Figs. 4 and 5).⁷⁵ Prolonged depolarization and influx of Na⁺ impedes the reuptake of glutamate and other excitatory amino acids, while Ca²⁺ influx may adversely affect the function of cell and mitochondrial membranes.⁷⁵

FIG. 5 Cascade of events elicited by bioenergetic failure and intracellular accumulation of calcium. Abbreviations as in Figure 4. Reprinted from Ref. No. 75 with permission.

Although reperfusion following brief to moderate periods of ischemia (10–15 min) should result in rapid repolarization, metabolic reactions set off during the original ischemic event can have downstream consequences that affect the ultimate survival of some cells.⁷⁵ Resumption of perfusion to tissue in which the precursors of free radicals have accumulated may induce oxidative stress, causing microvascular dysfunction and reperfusion damage. Glycolysis, initiated during bioenergetic failure by lack of oxygen, may give rise to excessive acidosis, particularly if an inadequate but low blood flow continues to deliver a supply of glucose.^{75,81} Acidosis can accelerate free radical production, interfere with the intracellular signal transduction pathway, activate endonucleases, and contribute to mitochondrial damage.⁸² Mitochondrial dysfunction during ischemia leads to further production of free radicals, which may then trigger secondary mitochondrial failure and cell death.⁷⁵ Secondary damage to mitochondria and brain tissue may occur after a delay of hours or days.⁷⁵

Ischemic Damage

Ischemic damage is complex and time dependent and is the result of a number of interrelated events that occur as a consequence of CBF failure. The immediate ischemic core can be salvaged only if blood flow is restored before irreversible injury occurs, usually within 1 or 2 h of the event at normothermia.⁸³ After that point, ionic imbalances perpetuate damage within the ischemic zone and reversal of ATP depletion is no longer possible.⁸³ Calcium has been implicated in a number of destructive interactions, including lipolysis, proteolysis, and activation of endonucleases that degrade DNA, which may trigger apoptosis of neurons.⁸³ Disruption of cellular Ca²⁺ homeostasis is believed to be one of the fundamental triggers in the neuronal death and dysfunction that results in clinical disability.⁸⁴

Disruption of the BBB, a known consequence of ischemia, leads to brain edema, which is a major complication of stroke and a critical determinant of outcome.⁸⁵ In the initial phase following ischemia, the BBB remains intact and, as the result of ionic gradient disruptions, brain cells swell, decreasing the extracellular space and causing cytotoxic edema.⁸⁵ As time goes on, however, the BBB becomes permeable, allowing an influx of plasma constituents, which leads to expansion of extracellular spaces and gives rise to vasogenic edema.⁸⁵

A compromised BBB also may allow an increase in the concentration of excitatory amino acids, which are believed to contribute to ischemic brain injury.^{85–87} Elevated extracellular levels of the excitatory neurotransmitter glutamate are believed to play an important role in ischemic injury. In the normal brain, cellular uptake of glutamate maintains extracellular levels below the neurotoxic threshold; under ischemic conditions, however, depletion of energy stores impedes this uptake.⁸⁸

The Penumbra

The ischemic penumbra, the region of brain tissue on the periphery of the actual infarct or ischemic core, is of signifi-

cant clinical and therapeutic relevance. The penumbra is perfused at higher CBF levels, but is vulnerable to many of the metabolic cascades that occur in the ischemic core.⁸⁹ Within the normal brain, glucose metabolism and CBF are closely coupled, a relationship that is disrupted by the ionic imbalances and spreading depression and depolarization that follow ischemia.⁸⁹

Damage within the penumbra occurs over time, possibly as the result of postischemic inflammation and cellular infiltration.⁸⁹ Compromised penumbral perfusion may also result in repeated episodes of focal hypoxia, possibly contributing to the gradual expansion of the infarct core. Oxygen-free radicals and extracellular glutamate may damage penumbral neurons.⁸⁹ Spreading depression and spontaneous waves of depolarization (SWD) in the penumbra during the acute phase of ischemia may be triggered by increases in glutamate and potassium or generated by focal depolarizations occurring in poorly perfused areas.⁸⁹ Edema may also play a role by lowering the threshold for SWD. Once elicited, SWD likely affects both the energy-stable regions and metabolically compromised ischemic core within the same cerebral hemisphere.^{89, 90} Depolarizations may induce or aggravate anaerobic metabolism, resulting in increases in lactic acid levels and acidosis and creating episodes of compromised energy metabolism within the penumbra.^{80, 91–93}

Imaging Studies

The advent of positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI) has allowed tremendous strides to be made in our understanding of the pathophysiology of ischemic stroke. Positron emission tomography permits the measure of glucose and oxygen metabolism and CBF following stroke, providing a detailed picture of the consequences of ischemia on brain metabolism. Studies have shown that during the 2 to 3 weeks following an ischemic event, blood flow increases within the ischemic region; however, no changes in either glucose or oxygen metabolism occur.^{3, 94} Apparently, significant anaerobic glycolysis continues despite adequate perfusion and delivery of both oxygen and glucose.^{3, 95} In vivo studies have indicated that about 1 month after the ischemic event, secondary declines in CBF and oxygen metabolism occur.^{3, 94, 96–98} Imaging studies have also provided information on the events occurring within the penumbra during ischemia, which indicates that spreading depression-like depolarizations occur within the peri-infarct region as well.⁸⁹ Using PET, it is clear that a time-dependent penumbra exists in acute ischemic stroke in humans and that earlier treatment, while there is still a large penumbra, is likely to be more effective in reducing ischemic damage than later treatment when the penumbra is shrinking or gone.

The potential for PET to provide a better understanding of both the pathophysiology of acute stroke and the clinical effects of treatments and to produce more accurate assessments of stroke damage is evident from the results of a number of small studies. In a study by Heiss *et al.* in 12 patients with acute stroke who underwent treatment with systemic recombi-

nant tissue plasminogen activator (rt-PA), PET scans done before or during and repeatedly after thrombolysis indicated a strong correlation between the volume of infarcted gray matter at 3 weeks and eventual clinical deficit. In patients with < 15 ml of severely hypoperfused (< 12 ml/100 g/min) gray matter on the first PET, full clinical recovery occurred, but in those with areas larger than 20 ml some degree of neurological deficit persisted. It is interesting that only 22.7% of gray matter that was severely hypoperfused on the initial PET ultimately became necrotic. Furthermore, areas of severe hypoperfusion that became reperfused at nearly normal levels predicted the extent to which clinical improvement occurred within 3 weeks, which suggests the importance of early reperfusion and the possible value of thrombolytic treatment.⁹⁹

A second study by Heiss *et al.* used PET to explore the value of a benzodiazepine receptor ligand as a marker to distinguish cortical areas that have suffered irreversible ischemic damage from viable penumbra tissue that may benefit from early reperfusion. Patients in whom areas of decreased [¹¹C] flumazenil binding were detected suffered permanent lesions that corresponded to the areas of benzodiazepine receptor deficit. However, with normal flumazenil binding, even large areas of hypoperfusion could be reversed with thrombolysis.¹⁰⁰

Unfortunately, each of the currently available imaging technologies has its limitations. Positron emission tomography is extremely sensitive, and its ability to provide information on hemodynamics and metabolic processes makes it a highly valuable research tool; however, its use is restricted by expense and the need for radioisotopes.¹⁰¹ Despite its ready availability in community hospitals, CT has limited application in acute stroke as well. Computed tomography acquires data from thin sections of tissue using an x-ray beam but is not as sensitive to hyperacute changes as MRI. Magnetic resonance imaging does not use ionizing radiation and is more useful in clinical practice for identifying hyperacute focal ischemic brain lesions—location, size, and degree of perfusion-diffusion mismatch that many experts believe represents the penumbral, potentially viable tissue. However, the long scan times may be difficult, because patients must remain immobile, a difficult prospect with an acutely ill stroke patient.¹⁰¹ This limitation is becoming less important as acute imaging pulse sequences are shortening the time for data acquisition and processing. The newer technologies of near infrared spectroscopy (NIRS) and functional MRI may provide better assessments and understanding of in vivo microcirculation in the near future.¹⁰²

Stroke Recurrence and the Need for Secondary Prevention

Approximately one of every six strokes is a recurrent stroke.^{11, 15} A prior stroke places a patient at considerable risk for recurrent ischemia, with the period immediately following the event posing the greatest risk. In the first 30 days, the cumulative risk for recurrent stroke is 3% to as high as 10%, and over the following year it ranges from 5 to 14%.¹⁰³ Between 25 and 29% of patients will suffer another stroke within 5

years of the first ischemic event.^{104, 105} Risk also exists for people who have had a TIA, with an average annual risk of 4% for stroke.²¹ The risk is greatest in the first year, especially in the first few weeks after the TIA.⁶⁷

Recent data have indicated that in patients who have had an initial ischemic event—either stroke or MI—the most likely subsequent ischemic event will be a stroke in 75% of stroke patients and an MI in 75% of those who have had an MI.⁴ Nearly one quarter of stroke victims die; most survivors sustain some degree of permanent disability. Given these high rates of death and disability, secondary stroke prevention is a primary focus in the medical management of these patients.

Therapeutic Targets

Unless contraindicated, antiplatelet agents are first-line treatment for secondary prevention of stroke,¹⁰⁶ in conjunction with aggressive control of established risk factors; however, a review of treatment for these risk factors is beyond the scope of this article. Antiplatelet agents, by inhibiting platelet aggregation, have demonstrated a reduction in the risk of stroke that ranges from 18% (primary outcome stroke or death; 95% confidence interval [CI] 0.67–0.99; $p = 0.02$) for aspirin alone, to 27% (primary outcome fatal or nonfatal stroke; 95% CI 6.6–42.3; $p = 0.011$) with ticlopidine, to 37% (primary outcome stroke; 95% CI 0.48–0.73; $p < 0.001$) with aspirin plus extended-release dipyridamole.^{107–109} Note that these amounts of risk reduction cannot be directly compared with each other, as the groups in each study were not necessarily similar in baseline characteristics, entrance criteria, and subsequent recurrent risk. The antiplatelet agent clopidogrel reduced relative risk 29% (odds ratio 0.71; 95% CI 0.58–0.86, $p = 0.0006$) for the combined endpoints of cardiovascular death, MI, or stroke, and cardiovascular death, MI, stroke, or refractory ischemia.¹¹⁰ In neither the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial nor Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) were the data provided only on the endpoint of stroke.^{110, 111}

Myocardial infarction and death from all causes are important endpoints as well, and several of the studies, in addition to the CURE study, included MI and/or death in their analysis. In the Second European Stroke Prevention Study (ESPS-2), the combined endpoint of stroke and/or death was reduced by 13% (95% CI 0.71–0.99) with aspirin alone, by 15% (95% CI 0.68–0.96) with dipyridamole alone, and by 24.3% (95% CI 0.59–0.84) with aspirin plus extended-release dipyridamole when compared with placebo. Death alone was reduced by 9.9% (95% CI 0.71–1.09) with aspirin, 6.9% (95% CI 0.74–1.13) with dipyridamole, and 8.4% (95% CI 0.73–1.12) with aspirin plus extended-release dipyridamole.¹⁰⁷ The Ticlopidine Aspirin Stroke Study (TASS) demonstrated a 12% reduction (95% CI 2–26%) for the primary endpoint of death from all causes or nonfatal stroke at 3 years (see Table I).¹⁰⁹

Both ticlopidine and clopidogrel prevent platelet aggregation induced by ADP. Ticlopidine's adverse reaction profile has limited its usefulness in clinical practice, with severe re-

TABLE I Reduction of events with antiplatelet therapy: Results of the major trials

Trial (Ref. No.)	No. of patients	Agents	Primary endpoint	Reduction in events
CAPRIE (111)	19,185	Clopidogrel 75 mg/day, aspirin 325 mg/day	Fatal and nonfatal vascular events	RRR 8.7% (clopidogrel vs. aspirin)
CURE (110)	2,392	Clopidogrel 75 mg/day, placebo, aspirin 75–325 mg/day	Vascular events	29% reduction clopidogrel vs. placebo; 10% reduction clopidogrel vs. aspirin
ESPS-2 (107)	6,602	Dipyridamole 200 mg b.i.d., aspirin 25 mg b.i.d., placebo, dipyridamole 200 mg b.i.d. + aspirin 25 mg b.i.d.	Stroke or death	37% RR for dipyridamole + aspirin vs. 18% RR for aspirin alone
SALT (108)	1,360	Aspirin 75 mg/day, placebo	Stroke or death	18% RR aspirin vs. placebo
TASS (109)	3,069	Ticlopidine 500 mg/day, aspirin 1300 mg/day	Fatal and nonfatal stroke	12% RRR
WARSS (141)	2,206	Warfarin 2 mg/day (INR 1.4–2.8), aspirin 325 mg/day	All cause death, recurrent ischemic stroke	No significant difference between the two treatments in event rate

Abbreviations: RRR = relative risk reduction, RR = risk reduction.

versible neutropenia occurring in just under 1% of those who take it.^{112,113} Although it is chemically related, clopidogrel appears to be safer than ticlopidine. A cyclooxygenase inhibitor, aspirin appears to inhibit platelet aggregation by suppressing thromboxane A.¹¹⁴

Several mechanisms of action have been suggested for extended-release dipyridamole, which may account for its benefit in stroke prevention in ESPS-2. Antiplatelet effects include inhibition of cellular uptake and metabolism of adenosine, inhibition of cyclic AMP phosphodiesterase, and inhibition of cyclic GMP phosphodiesterase.¹¹⁴ There are indications that dipyridamole may exert antithrombotic effects via the vessel wall¹¹⁵ and exhibit antioxidant properties. Increased synthesis of 13-hydroxyoctadecadienoic acid (HODE) by the vascular endothelium has been noted with dipyridamole administration in animal models and appears to interact with cAMP levels to influence vessel wall thrombogenicity.¹¹⁵ Animal experimentation has demonstrated that dipyridamole, but not other antithrombotic drugs, decreased platelet-derived growth factor levels and inhibited vascular smooth muscle cell proliferation.^{115–117}

Perhaps because the mechanisms of action of aspirin and dipyridamole differ considerably, the combination of these two agents appears to have an additive effect in preventing stroke, as seen in ESPS-2 (Fig. 6).¹¹⁸

Recent evidence suggests that angiotensin-converting enzyme (ACE) inhibitors may have beneficial effects on the vascular endothelium. Although they are better known for their antihypertensive effects, these agents may help mediate NO synthesis and release as well.¹¹⁹ Studies have indicated that NO synthase expression can be regulated by shear stress, oxidized LDL, lysophosphatidyl choline, hypoxia, and manipulation of the activity of protein kinase C.¹¹⁹ Results of the

Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that the ACE inhibitor ramipril lowered the risk of stroke by 33% in hypertensive diabetics. A reduction of 25% for the combined endpoint of MI, stroke, or cardiovascular death after adjusting for blood pressure measurements was observed.¹²⁰ However, when compared with a diuretic as monotherapy for hypertension, ACE inhibition does not appear to be as effective in reducing the risk of stroke. The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial found no difference in the primary outcome of combined fatal coronary heart disease or nonfatal myocardial infarction or for the secondary outcome of all-cause mortality in subjects treated with the diuretic chlorthalidone, the calcium-channel blocker amlodipine, or the ACE inhibitor lisinopril over a 4- to 8-year follow-up (mean follow-up 4.9 years).¹²¹ Lisinopril had a 33.3% 6-year rate of combined cardiovascular disease, which included the endpoint of

FIG. 6 Mechanism of action. PDE = phosphodiesterase, ADP = adenosine diphosphate, COX = cyclooxygenase, TXA = thromboxane A₂.

stroke, compared with a 30.9% rate with chlorthalidone (relative risk, 1.10; 95% CI 1.05–1.16).¹²¹ Stroke was a definite endpoint in the ALLHAT trial. The thiazide diuretic chlorthalidone was superior to the ACE inhibitor lisinopril for prevention of stroke.

Dyslipidemia is a risk factor for cardiovascular disease; therefore, cholesterol levels, particularly elevated LDL, are valid therapeutic targets for secondary prevention of stroke. Statins may reduce the risk of stroke by up to 25%.¹²² There is evidence that these agents may have beneficial effects on carotid artery stenosis progression as well.^{123, 124} However, as with the ACE inhibitors, the statins also may provide cardiovascular benefits in addition to their lipid-lowering efficacy. Statins appear to have anti-inflammatory and antiproliferative effects that may prove clinically relevant in the treatment of atherosclerosis.¹²⁵

Since many patients with cerebrovascular disease are on statins, the recent report of a possible important drug interaction between atorvastatin and the antiplatelet agent clopidogrel may be especially important. Because both agents use the CYP3A4 metabolic pathway, use of atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation.¹²⁶ This may have clinical relevance, although it remains to be proven.

Surgical Options

In patients with severe extracranial internal carotid artery stenosis (70–99%) and symptomatic disease, carotid endarterectomy (CEA) provides significant benefit in stroke prevention, with an absolute risk reduction of 17.7% ($p = 0.004$).¹²⁷ However, benefit is maintained only if the surgical complication rate is $< 6\%$. Risk of perioperative stroke or death was increased by female gender, age > 75 years, systolic blood pressure > 180 mmHg, and a history of peripheral vascular disease.¹²² Carotid endarterectomy for asymptomatic disease is more controversial and should be contemplated only in patients with carotid stenosis of 60 to 99% when surgery can be performed with a combined stroke or death rate of $< 3\%$.¹²⁸ Absolute risk reduction is about 1% per year during the 5 years following surgery.

Carotid angioplasty and stenting are sometimes utilized in patients for whom CEA may be considered too risky. A trial by Vitek *et al.* of carotid artery stenting in 451 vessels (390 patients) demonstrated a reduction in stenosis from 74 to 5%. Technical success was achieved in 98% of cases, although the combined death and stroke rate at 30 days was high (7.9%).¹²⁹ Antiplatelet therapy before and after stenting is recommended.¹²⁹ Angioplasty and stenting of the intracranial carotid and vertebrobasilar arteries have also been performed in patients who have otherwise failed medical management.^{130–131} However, angioplasty and stenting for cerebrovascular disease is unproven. Currently, the National Institutes of Health (NIH)-funded clinical trial Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is being conducted. Patients for whom angioplasty/stenting is contemplated should be considered for enrollment in a clinical trial, such as CREST, whenever possible.

Although asymptomatic patent foramen ovale (PFO) may be found in nearly one-third of the population, the prevalence of PFO in patients with cryptogenic stroke suggests that there may be an association, particularly when a large PFO or PFO with an increased right-to-left shunt is found.^{132, 133} Recent evidence suggests that treatment may reduce some of the increased risk associated with PFO. Investigators from the PFO in Cryptogenic Stroke Study (PICSS) examined the role of PFO in 630 stroke patients assigned to warfarin or aspirin. Patent foramen ovale was found in 203 (33.8%) patients. No significant difference was noted in time to the primary endpoints of recurrent ischemic stroke or death between those with and those without PFO (95% CI 0.62–1.48; $p = 0.84$; 2-year event rates 14.8 vs. 15.4%), nor was any difference noted within the subset of patients who had experienced a cryptogenic stroke (95% CI 0.60–2.37; $p = 0.65$; 2-year event rates 14.3 vs. 12.7%). The size of the PFO had no significant effect on the event rate, and results from the aspirin and warfarin cohorts were similar as well.¹³⁴ The authors concluded that in patients receiving antiplatelet or anticoagulant therapy, the presence of PFO did not increase the likelihood of adverse events.^{132, 134} In patients aged < 50 to 60 years, who have had a cryptogenic stroke, who have a large PFO with significant interatrial shunting, and who have recurrent ischemic events despite antiplatelet therapy, anticoagulation may prove beneficial. However, PFO endovascular closure is an option in patients who do not wish to be maintained on lifelong anticoagulation or who cannot tolerate such therapy.¹³² This form of therapy is unproven and is the basis of an ongoing clinical trial in young persons with otherwise cryptogenic stroke.

Therapy for Acute Ischemic Stroke

The efficacy of intravenous t-PA administration within the first 3 h of acute ischemic stroke onset has been established.^{135–139} Intra-arterial thrombolytic therapy up to 6 h after large MCA strokes due to documented occlusion of the proximal MCA has also been shown to be beneficial.¹⁴⁰ The investigations into the metabolic disturbances attendant with focal cerebral ischemia suggest other targets as well. Unfortunately, despite the numerous targets identified as involved in the ischemic cascade, all clinical trials with neuroprotection to date have failed to establish efficacy, in part because of trial design. Often the time window within which treatment was given was too long.

Conclusions

Ischemic stroke has a devastating effect on cerebral homeostasis, with inadequate perfusion resulting in bioenergetic failure. Damage appears to be mediated through oxygen/metabolism uncoupling, spreading depression and depolarization, ionic imbalances, increasing extracellular glutamate concentrations, and intracellular Ca^{2+} increases. Over time, the ischemic

core can spread into the marginally affected penumbra, increasing the clinical damage and neurological deficit; hence, this is a key factor in delivering treatment for acute stroke.

Although there are promising avenues for research into additional therapeutic strategies for acute stroke, our most efficacious therapies remain preventative. Lifestyle modifications, control of hypertension, hyperglycemia, and hyperlipidemia, smoking cessation, and treatment of cardiac condition are primary as well as secondary preventive strategies. Furthermore, once a stroke has occurred, antiplatelet therapy can significantly reduce the risk of secondary stroke.

References

1. Rajamani K, Fisher M: An overview of atherosclerosis. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 324–329. San Diego, Calif.: Academic Press, 1997
2. Roberts WC: The coronary arteries in ischemic heart disease: Facts and fancies. *Triangle* 1977;16:77–90
3. Greenberg JH: Glucose and oxygen metabolism in ischemia. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 227–248. Malden, Mass.: Blackwell Science, 1998
4. Vickrey BG, Rector TS, Wickstrom SL, Guzy PM, Sloss EM, Gorelick PB, Garber S, McCaffrey DF, Dake MD, Levin RA: Occurrence of secondary ischemic events among persons with atherosclerotic vascular disease. *Stroke* 2002;33:901–906
5. Joint National Committee: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;24:2413–2446
6. Elliott WJ, Bakris GL, McCampbell EL, Prisant LM: Diabetic hypertension. Ensuring optimal therapy in the primary-care setting. Medical Crossfire. Available at: www.medicalcrossfire.com/debate_archive/Spec_Ed/DiabeticHypertension.htm. Accessed October 16, 2002
7. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, Hill M, Howard G, Howard VJ, Jacobs B, Levine SR, Mosca L, Sacco RL, Sherman DG, Wolf PA, del Zoppo GJ: AHA Scientific Statement. Primary prevention of ischemic stroke. *Circulation* 2001;103:163–182
8. Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
9. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
10. Blauw GJ, Lagaay AM, Smelt AHM, Westendorp RGJ: Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. *Stroke* 1997;28:946–950
11. American Heart Association. Available at: www.americanheart.org. Accessed March 13, 2003.
12. Sloan MA: Toxicity/substance abuse. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 413–416. San Diego, Calif.: Academic Press, 1997
13. Kittner SJ, Bush TL: Pregnancy, hormonal contraception, and postmenopausal estrogen replacement therapy. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 324–329. San Diego, Calif.: Academic Press, 1997
14. Women's Health Initiative Writing Group: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: First results of the WHI in the HT study. *J Am Med Assoc* 2002;288:321–333
15. American Stroke Association. Available at www.strokeassociation.jhtm?identifier=1033. Accessed December 6, 2002.
16. Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, Barrett-Connor E, Hulley SB, for the HERS Research Group: Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638–642
17. Viscou CM, Brass LM, Kernan WN, Sarrel PM, Suissa SM, Horwitz RI: A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243–1249
18. Kloner RA, Hale S, Alker K, Rezkalla S: The effects of acute and chronic cocaine use on the heart. *Circulation* 1992;85:407–419
19. Mohr JP, Albers GW, Amarenco P, Babikian VL, Biller J, Brey RL, Coull B, Easton JD, Gomez CR, Helgason CM, Kase CS, Pullicino PM, Turpie AGG: American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. Etiology of stroke. *Stroke* 1997;28:1501–1506
20. Hart RC, Albers GW, Koudstaal PJ: Cardioembolic stroke. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 1392–1429. Malden, Mass.: Blackwell Science, 1998
21. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA: Risk factors. American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. *Stroke* 1997;28:1507–1517
22. Wolf PA, Abbott RD, Kannel WB: Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991;22:983–988
23. Helgason CM, Wolf PA: Executive summary. American Heart Association Prevention Conference IV: Prevention and rehabilitation of stroke. *Circulation* 1997;96:701–707
24. Sacco RL: Current epidemiology of stroke. In *Current Review of Cerebrovascular Disease* (Eds. Fisher M, Bogousslavsky J), p. 3–14. Philadelphia, Pa.: Current Medicine, 1993
25. Mohr JP: Natural history and pathophysiology of brain infarction. *Circulation* 1991;83(suppl I):I-172–I-175
26. Sacco RL, Ellenberg JA, Mohr JP, Tatemichi TK, Hier DB, Price TR, Wolf PA: Infarction of undetermined cause: The NINCDS Stroke Data Bank. *Ann Neurol* 1989;25:382–390
27. Tresser SJ, Selman WR, Ratcheson RA: Pathophysiological alterations following aneurysm rupture. In *Ruptured Cerebral Aneurysms: Perioperative Management*. Vol. 6: *Concepts in Neurosurgery* (Eds. Ratcheson RA, Wirth FP), p. 23–45. Baltimore, Md.: Williams and Wilkins, 1994
28. Chicoine MR, Dacey RG Jr: Clinical aspects of subarachnoid hemorrhage. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 425–432. San Diego, Calif.: Academic Press, 1997
29. Voelker JL, Kaufman HH: Clinical aspects of intracerebral hemorrhage. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 432–436. San Diego, Calif.: Academic Press, 1997
30. Broderick JP, Brott T, Tomsick T, Miller R, Huster G: Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. *J Neurosurg* 1993;78:188–191
31. Sacco R: Ischemic stroke. In *Handbook of Neuroepidemiology* (Eds. Gorelick PB, Alter M), p. 77–119. New York, N.Y.: Marcel Dekker, 1994
32. Mohr JP: Cryptogenic stroke. *N Engl J Med* 1988;318:1197–1198
33. Heinzlef O, Cohen A, Amarenco P: An update on aortic causes of ischemic stroke. *Curr Opin Neurol* 1997;10:64–72
34. Barbut D, Caplan LR: Cerebrovascular complications of cardiac surgery. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 783–786. San Diego, Calif.: Academic Press, 1997

35. Sawada T: Anterior cerebral artery and anterior communicating artery syndromes. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 986–996. Malden, Mass.: Blackwell Science, 1998
36. Neau J-PH, Bogousslavsky J: Middle cerebral artery syndromes. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 997–1027. Malden, Mass.: Blackwell Science, 1998
37. Caplan LR, Bogousslavsky J: Posterior cerebral artery syndromes. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 1028–1056. Malden, Mass.: Blackwell Science, 1998
38. Donnan GA, Yasaka M: Lacunes and lacunar syndromes. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 1090–1102. Malden, Mass.: Blackwell Science, 1998
39. Sacco SE, Whisnant JP, Broderick JP, Phillips SJ, O'Fallon WM: Epidemiological characteristics of lacunar infarcts in a population. *Stroke* 1991;22:1236–1241
40. Bernat JL: Systemic hypoperfusion brain injury. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B), p. 289–292. San Diego, Calif.: Academic Press, 1997
41. Bladin CF, Chambers BR: Clinical features, pathogenesis, and computed tomographic characteristics of internal watershed infarction. *Stroke* 1993;24:1925–1932
42. Bladin CF, Chambers BR: Frequency and pathogenesis of hemodynamic stroke. *Stroke* 1994;25:2179–2182
43. Albers GW: Transient ischemic attack—proposal for a new definition. *N Engl J Med* 2002;21:347:1713–1716
44. Carolei A, Marini C, Fieschi C: Transient ischemic attacks. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 941–960. Malden, Mass.: Blackwell Science, 1998
45. Ad Hoc Committee on Cerebrovascular Diseases: Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990;21:637–676
46. Brown RD Jr, Petty GW, O'Fallon WM, Wiebers DO, Whisnant JP: Incidence of transient ischemic attack in Rochester, Minnesota, 1985–1989. *Stroke* 1998;29:2109–2113
47. Johnston SC, Gress DR, Browner WS, Sidney S: Short-term prognosis after emergency department diagnosis of TIA. *J Am Med Assoc* 2000;284:2901–2906
48. Iannuzzi A, Wilcosky T, Mercuri M, Rubba P, Bryan FA, Bond MG: Ultrasonographic correlates of carotid atherosclerosis in transient ischemic attack and stroke. *Stroke* 1995;26:614–619
49. Hollander M, Breteler MMB: Markers of subclinical vascular disease and stroke. In *The Prevention of Stroke* (Eds. Gorelick PB, Alter M), p. 105–114. New York, N.Y.: Parthenon Publishing Group, 2002
50. Strong JP: Atherosclerotic lesions. Natural history, risk factors, and topography. *Arch Pathol Lab Med* 1992;116:1268–1275
51. Rajamani K, Fisher M, Fisher M: Atherosclerosis, pathogenesis and pathophysiology. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 1308–1318. Malden, Mass.: Blackwell Science, 1998
52. Pepine CJ: The effects of angiotensin-converting enzyme inhibition on endothelial dysfunction: Potential role in myocardial ischemia. *Am J Cardiol* 1998;9(suppl 2):23S–27S
53. Becker RC: Antithrombotic therapy after myocardial infarction. *N Engl J Med* 2002;347:1019–1022
54. Faraci FM, Heistad DD: Pathophysiologic mechanisms in cerebral blood vessels. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 333–342. Malden, Mass.: Blackwell Science, 1998
55. Johansson BB: Hypertension. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B), p. 142–144. San Diego, Calif.: Academic Press, 1997:142–144
56. Sawada K, Naiki M, Yago H, Matsushita K, Ohtsuki T, Kitagawa K, Matsumoto M, Hori Masatsugu: Hypertension associated with reduced plasma thrombomodulin levels and a hypercoagulable state in rats. *Clin Exp Hypertens* 2003;25:73–84
57. Nishikawa T, Edelstein D, Brownlee M: The missing link: A single unifying mechanism for diabetic complications. *Kidney Int* 2000;58(suppl 77):S26–S30
58. DeGraba TJ: Inflammation, infection and homocysteine in atherosclerosis. In *The Prevention of Stroke* (Eds. Gorelick PB, Alter M), p. 49–64. New York, N.Y.: Parthenon Publishing Group, 2002
59. Marfella R, Esposito K, Giunta R, Coppola G, De Angelis L, Farzati B, Paolisso G, Giugliano D: Circulating adhesion molecules in humans: Role of hyperglycemia and hyperinsulinemia. *Circulation* 2000;101:2247–2251
60. Ross R, Wight TN, Strandness E, Thiele B: Human atherosclerosis: I. Cell constituents and characteristics of advanced lesions of the superficial femoral artery. *Am J Pathol* 1984;114:79–93
61. Cushing SD, Berliner JA, Valente AJ, Territo MC, Navab M, Parhami F, Gerrity R, Schwartz CJ, Fogelman AM: Minimally modified low-density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. *Proc Natl Acad Sci USA* 1990;87:5134–5138
62. Quinn MT, Parthasarathy S, Fong LG, Steinberg D: Oxidatively modified low-density lipoproteins: A potential role in recruitment and retention of monocyte/macrophages during atherogenesis. *Proc Natl Acad Sci USA* 1987;84:2995–2998
63. Quinn MT, Parthasarathy S, Steinberg D: Endothelial cell-derived chemotactic activity for mouse peritoneal macrophages and the effects of modified forms of low-density lipoprotein. *Proc Natl Acad Sci USA* 1985;82:5949–5953
64. Kugiyama K, Bucay M, Morrisett JD, Roberts R, Henry PD: Oxidized LDL impairs endothelium-dependent arterial relaxation. *Circulation* 1989;80(suppl II):II-279
65. Sacco RL, Elkind M, Boden-Albala B, Lin I-F, Kargman DE, Hauser WA, Shea S, Paik MC: The protective effect of moderate alcohol consumption on ischemic stroke. *J Am Med Assoc* 1999;281:53–60
66. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, Ross JL, Raps E, Ozer MN, Brass LM, Malone ME, Goldberg S, Booss J, Hanley DF, Toole JF, Greengold NL, Rhew DC: Prevention of a first stroke: A review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *J Am Med Assoc* 1999;281:1112–1120
67. Sacco RL: Risk factors, outcomes, and stroke subtypes for ischemic stroke. *Neurology* 1997;49(suppl 4):S39–S44
68. Wolf PA: Cigarettes, alcohol, and stroke. *N Engl J Med* 1986;315:1087–1089
69. Gorelick PB: Stroke prevention therapy beyond antithrombotics: Unifying mechanisms in ischemic stroke pathogenesis and implications for therapy. An invited review. *Stroke* 2002;33:862–875
70. Miller A, Mujumdar V, Shek E, Guillot J, Angelo M, Palmer L, Tyagi SC: Hyperhomocyst(e)inemia induces multiorgan damage. *Heart Vessels* 2000;15:135–143
71. Feinberg WM, Coull BM: Coagulopathies and stroke. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B), p. 399–401. San Diego, Calif.: Academic Press, 1997
72. Anderson LR, Feinberg WM: Primary platelet disorders. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B), p. 401–405. San Diego, Calif.: Academic Press, 1997
73. Brey RL, Stallworth CL, McGlasson DL, Wozniak MA, Wityk RJ, Stern BJ, Sloan MA, Sherwin R, Price TR, Macko RF, Johnson CJ, Earley CJ, Buchholz DW, Hebel JR, Kittner SJ: Antiphospholipid antibodies and stroke in young women. *Stroke* 2002;33:2396–2400
74. Brey RL, Abbott RD, Curb JD, Sharp DS, Ross GW, Stallworth CL, Kittner SJ: β_2 -glycoprotein 1-dependent anticardiolipin antibodies and risk of ischemic stroke and myocardial infarction: The Honolulu Heart Program. *Stroke* 2001;32:1701–1706
75. Siesjö BK, Kristian T, Katsura K-I: Overview of bioenergetic failure and metabolic cascades in brain ischemia. In *Cerebrovascular*

- Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 3–13. Malden, Mass.: Blackwell Science, 1998
76. Schmid-Schonbein GW: Capillary plugging by granulocytes and no reflow phenomenon in the microcirculation. *Federation Proc* 1987;46:2397–2401
 77. del Zoppo GJ: Microvascular changes during cerebral ischemia and reperfusion. *Cerebrovasc Brain Metab Rev* 1994;6:47–96
 78. Feuerstein GZ, Liu T, Barone FC: Cytokines, inflammation, and brain injury: Role of tumor necrosis factor. *Cerebrovasc Brain Metab Rev* 1994;6:341–360
 79. Hallenbeck J: Inflammatory reactions at the blood-endothelial interface in acute stroke. In *Advances in Neurology* (Eds. Siesjö B, Wieloch T), p. 281–296. New York: Raven Press, 1996
 80. Betz AL: Alterations in cerebral endothelial cell function in ischemia. In *Advances in Neurology* (Eds. Siesjö B, Wieloch T), p. 301–313. New York: Raven Press, 1996
 81. Siesjö BK, Katsura K, Mellergård P, Ekholm A, Lundgren J, Smith M-L: Acidosis-related brain damage. In *Progress in Brain Research* (Eds. Kogure K, Hossmann K-A, Siesjö BK), p. 23–48. Amsterdam, Netherlands: Elsevier Science, 1993
 82. Siesjö BK, Katsura KI, Kristián T, Li PA, Siesjö P: Molecular mechanisms of acidosis-mediated damage. *Acta Neurochir Suppl* 1996;66:8–14
 83. Hossmann K-A: Thresholds of ischemic injury. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 193–204. Malden, Mass.: Blackwell Science, 1998
 84. Tymianski M: The central role of calcium ions and calcium-permeable channels in ischemic brain injury. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 371–390. Malden, Mass.: Blackwell Science, 1998
 85. Betz AL, Dietrich WD: Blood-brain barrier dysfunction in cerebral ischemia. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 358–370. Malden, Mass.: Blackwell Science, 1998
 86. Choi DW: Glutamate neurotoxicity and disease of the nervous system. *Neuron* 1988;1:623–634
 87. Rothman SM, Olney JW: Excitotoxicity and the NMDA receptor—still lethal after eight years. *Trends Neurosci* 1987;10:299–302
 88. Welsh FA: Ischemic energy failure. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 217–226. Malden, Mass.: Blackwell Science, 1998
 89. Back T, Nedergaard M, Ginsberg MD: The ischemic penumbra. In *Cerebrovascular Disease: Pathophysiology, Diagnosis, and Management* (Eds. Ginsberg M, Bogousslavsky J), p. 276–286. Malden, Mass.: Blackwell Science, 1998
 90. Takeda Y, Jacewicz M, Takeda Y, Nowak TS Jr, Pulsinelli WA: DC-potential and energy metabolites in focal ischemia. *J Cereb Blood Flow Metab* 1993;13(suppl 1):S450
 91. Back T, Hoehn-Berlage M, Kohno K, Hossmann K-A: Diffusion nuclear magnetic resonance imaging in experimental stroke: Correlation with cerebral metabolites. *Stroke* 1994;25:494–500
 92. Gyngell ML, Busch E, Schmitz B, Kohno K, Back T, Hoehn-Berlage M, Hossmann K-A: Evolution of acute focal cerebral ischemia in rats observed by localised 1H-MRS, diffusion-weighted MRI, and electrophysiological monitoring. *NMR Biomed* 1995;8: 206–214
 93. Gyngell ML, Back T, Hoehn-Berlage M, Kohno K, Hossmann K-A: Transient cell depolarization after permanent middle cerebral artery occlusion: An observation by diffusion-weighted MRI and localized 1H-MRS. *Magn Reson Med* 1994;31:337–341
 94. Heiss W-D, Huber M, Fink GR, Herholz K, Pietrzyk U, Wagner R, Wienhard K: Progressive derangement of peri-infarct viable tissue in ischemic stroke. *J Cereb Blood Flow Metab* 1992;12:193–203
 95. Baron JC, Lebrun-Grandie P, Collard P, Crouzel C, Mestelan G, Bousser MG: Noninvasive measurement of blood flow, oxygen consumption, and glucose utilization in the same brain regions in man by positron emission tomography: Concise communication. *J Nucl Med* 1982;23:391–399
 96. Lenzi GL, Jones T, McKenzie CG, Moss S: Non-invasive regional study of chronic cerebrovascular disorders using the oxygen-15 inhalation technique. *J Neurol Neurosurg Psychiatry* 1978;41:11–17
 97. Frackowiak RSJ: Pathophysiology of human cerebral ischemia: studies with positron tomography and 15oxygen. In *Brain Imaging and Brain Function* (Ed. Sokoloff L), p. 139–161. New York: Raven Press, 1985
 98. Baron JC, Rougement D, Lebrun-Grandie P, Bousser MG, Cabanis E, Bories J, Comar D, Castaigne P: Measurement of local blood flow and oxygen consumption in evolving irreversible cerebral infarction: An in vivo study in man. In *Cerebral Vascular Disease*, 4th ed. (Eds. Meyer JS, Lechner H, Reivich M, Ott EO), p. 205–212. Princeton, N.J.: Excerpta Medica, 1983
 98. Heiss W-D, Grond M, Thiel A, Stockhausen H-M, Rudolf J, Ghaemi M, Lottgen J, Stenzel C, Pawlik G: Tissue at risk of infarction rescued by early reperfusion: A positron emission tomography study in systemic recombinant tissue plasminogen activator thrombolysis of acute stroke. *J Cereb Blood Flow Metab* 1998;18: 1298–1307
 100. Heiss W-D, Kracht L, Grond M, Rudolf J, Bauer B, Wienhard K, Pawlik G: Early [11C] flumazenil/H₂O positron emission tomography predicts irreversible ischemic cortical damage in stroke patients receiving acute thrombolytic therapy. *Stroke* 2000;31:366–369
 101. Knight RA, Chopp M: Imaging techniques for focal ischemic damage. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B), p. 136–141. San Diego, Calif.: Academic Press, 1997
 102. Dirnagl U: Measurements of microcirculatory events in the brain in vivo. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B), p. 133–136. San Diego, Calif.: Academic Press, 1997
 103. National Stroke Association: Stroke Statistics. Available at www.stroke.org/brain_stat.cfm. Accessed February 24, 2003.
 104. Sacco RL: Ischemic stroke. In *Handbook of Neuroepidemiology* (Eds. Gorelick PB, Alter MA), p. 77–119. New York: Marcel Dekker, 1994
 105. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Survival and recurrence after first cerebral infarction: A population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology* 1998;50:208–216
 106. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P: Anti-thrombotic and thrombolytic therapy for ischemic stroke. *Chest* 2001;119:300S–320S
 107. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A: European Stroke Prevention Study 2: Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143:1–13
 108. SALT Collaborative Group: Swedish Aspirin Low-dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* 1991;338:1345–1349
 109. Ticlopidine Aspirin Stroke Study Group: Ticlopidine versus aspirin for stroke prevention: On-treatment results from the ticlopidine aspirin stroke study. *J Stroke Cerebrovasc Dis* 1993;3:169–176
 110. Mehta SR, Yusuf S, CURE Study Investigators: The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme: Rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J* 2000;21:2033–2041
 111. CAPRIE Steering Committee: A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329–1339
 112. Albers GW, Hart RG, Lutsep HL, Newell DW, Sacco RL: Supplement to the guidelines for the management of transient ischemic attacks. A statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. *Stroke* 1999;30:2502–2511

113. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, Yarnold PR, Kwaan HC, Green D: Thrombotic thrombocytopenic purpura associated with ticlopidine: A review of 60 cases. *Ann Intern Med* 1998;128:541–544
114. Taylor DW, Barnett HJM, Hayes RB, Ferguson GG, Sackett DL, Thorpe KE, Simard D, Silver FL, Hachinski V, Clagett GP, Barnes R, Spence JD, for the ASA and Carotid Endarterectomy (ACE) Trial Collaborators: Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: A randomised controlled trial. *Lancet* 1999;353:2179–2184
115. Eisert WG: Dipyridamole. In *Platelets* (Ed. Michelson AD), p. 803–815. San Diego, Calif.: Academic Press, 2002
116. Takehara K, Igarashi A, Ishibashi Y: Dipyridamole specifically decreases platelet derived growth factor release from platelets. *Thromb Res* 1990;12(suppl):73–79
117. Takehara K, Grotendorst GR, Silver R, LeRoy EC: Dipyridamole decreases platelet-derived growth factor levels in human serum. *Arteriosclerosis* 1987;7:152–155
118. The ESPS Group: The European Stroke Prevention Study (ESPS): Principal end-points. *Lancet* 1987;2:1351–1354
119. Rajagopalan S, Harrison DG: Reversing endothelial dysfunction with ACE inhibitors. *Circulation* 1996;94:240–243
120. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259
121. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium-channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc* 2002;288:2981–2997
122. Straus SE, Majumdar SR, McAlister FA: New evidence for stroke prevention. *J Am Med Assoc* 2002;288:1388–1398
123. Furberg CD, Adams HP Jr, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA, Young B, for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group: Effects of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 1994;90:1679–1687
124. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu C-r, Liu C-h, Alaupovic P, Kwong-Fu H, Azen SP: Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: A randomized, controlled clinical trial. *Ann Intern Med* 1996;124:548–556
125. Dichtl W, Dulak J, Frick M, Alber HF, Schwarzacher SP, Ares MPS, Nilsson J, Pachinger O, Weidinger F: HMG-CoA reductase inhibitors regulate inflammatory transcription factors in human endothelial and vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2003;23:58–63
126. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, Tait AR, Carville DGM, Guyer KE, Bates ER: Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation. A new drug–drug interaction. *Circulation* 2003;107:32–37
127. Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR, for the Veterans Affairs Cooperative Studies Program 309 Trialist Group: Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *J Am Med Assoc* 1991;266:3289–3294
128. Cohen SN: Carotid endarterectomy for asymptomatic disease. *J Stroke Cerebrovasc Dis* 1997;6:180–184
129. Vitek JJ, Roubin GS, Al-Mubarek N, New G, Iyer SS: Carotid artery stenting: Technical considerations. *Am J Neuroradiol* 2002;21:1736–1743
130. Gomez CR, Misra VK, Liu MW, Wadlington VR, Terry JB, Tulyapronchote R, Campbell MS: Elective stenting of symptomatic basilar artery stenosis. *Stroke* 2000;31:95–99
131. Mori T, Kazita K, Chokyu K, Mima T, Mori K: Short-term arteriographic and clinical outcome after cerebral angioplasty and stenting for intracranial vertebrobasilar and carotid atherosclerotic occlusive disease. *Am J Neuroradiol* 2000;21:249–254
132. Schneck MJ: Anticoagulation for stroke prevention. In *The Prevention of Stroke* (Eds. Gorelick PB, Alter M), p. 208–221. New York, N.Y.: Parthenon Publishing, 2002
133. Devuyst G, Bogousslavsky J: Status of patent foramen ovale, atrial septal aneurysm, atrial septal defect and aortic arch atheroma as risk factors for stroke. *Neuroepidemiology* 1997;16:217–223
134. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP, PFO in Cryptogenic Stroke Study (PICSS) Investigators: Effect of medical treatment in stroke patients with patent foramen ovale: Patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625–2631
135. Zivin JA: Emerging treatments for stroke. In *Primer on Cerebrovascular Diseases* (Eds. Welch KMA, Caplan LR, Reis DJ, Siesjo BK, Weir B), p. 791–793. San Diego, Calif.: Academic Press, 1997
136. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA: Intravenous tissue-type plasminogen activator for treatment of acute stroke: The Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *J Am Med Assoc* 2000;283:1145–1150
137. Grond M, Stenzel C, Schmulling S, Rudolf J, Neveling M, Lechleuthner A, Schneeweis S, Heiss WD: Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke* 1998;29:1544–1549
138. Hachinski AV, Hill MD, Buchan AM: The Canadian Activase for Stroke Effectiveness Study (CASES): Final results (abstr). *Cerebrovasc Dis* 2002;13(suppl 3):99
139. Wang DZ, Rose JA, Honings DS, Garwacki DJ, Milbrandt JC: Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. *Stroke* 2000;31:77–81
140. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F, for the PROACT (Prolyse in Acute Cerebral Thromboembolism) Investigators: Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. *J Am Med Assoc* 1999;282:2003–2011
141. Mohr JP, Thompson JLP, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P, for the Warfarin–Aspirin Recurrent Stroke Study Group: A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444–1451